Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene

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Objectives: Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) are ubiquitous toxic environmental contaminants. Prenatal and early life exposures affect pubertal events in experimental animals. We studied whether prenatal or lactational exposures to background levels of PCBs or DDE were associated with altered pubertal growth and development in humans.

Study design: Follow-up of 594 children from an existing North Carolina cohort whose prenatal and lactational exposures had previously been measured. Height, weight, and stage of pubertal development were assessed through annual mail questionnaires.

Results: Height of boys at puberty increased with transplacental exposure to DDE, as did weight adjusted for height; adjusted means for those with the highest exposures (maternal concentration 4+ ppm fat) were 6.3 cm taller and 6.9 kg larger than those with the lowest (0 to 1 ppm). There was no effect on the ages at which pubertal stages were attained. Lactational exposures to DDE had no apparent effects; neither did transplacental or lactational exposure to PCBs. Girls with the highest transplacental PCB exposures were heavier for their heights than other girls by 5.4 kg, but differences were significant only if the analysis was restricted to white girls.

Conclusions: Prenatal exposures at background levels may affect body size at puberty. (J Pediatr 2000;136:490-6)

The primary breakdown product of the insecticide DDT, dichlorodiphenyl dichloroethene, is now ubiquitous in the environment. Polychlorinated biphenyls are a group of compounds with numerous industrial uses, the major ones being in electrical equipment; they are also widespread in the environment despite the fact that their primary use was in closed systems. Both PCBs and DDE are lipophilic compounds that bioaccumulate and are found in most humans today. Both have the potential to interfere with hormonal function; estrogenic, anti-estrogenic, and anti-androgenic activities have been shown.[1-3]

DDE	Dichlorodiphenyl dichloroethene
PCBs	Polychlorinated biphenyls
ppm	parts per million

Impacts of both groups of compounds on pubertal events in experimental animals after exposures early in life have been reported; these include both delays and accelerations of pubertal events and effects on pubertal body weight. The DDT family has been associated with inconsistent pubertal effects. Exposure of young female rats to o,p'-DDT produced accelerations in some studies but not others[4-8]; body weight at approximately the time of puberty was unaffected,[5,6] although increases in weight at autopsy were seen in some cases.[7,8] Other DDT compounds had no effect.[8] Delays were reported after prenatal plus lactational exposure of female rats to o,p'-DDD; other DDT compounds had no effect.[8] Accelerations have been reported after prenatal exposure of female dogs to a DDT mixture.[9] One study reported delays after postnatal treatment of male rats with p,p'-DDE; at puberty exposed rats were heavier.[3] Another study reported no effects on the timing of pubertal events after prenatal plus lactational exposure of male and female rats to p,p'-DDE.[10]

PCBs have also been associated with inconsistent pubertal effects in female

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animals. Accelerations have been reported after early postnatal exposure to some PCB mixtures but not others.[11] One study reported both accelerations and delays after prenatal exposure, lactational exposure, or both; body weights for a period that included puberty were depressed.[12] Another reported delays after prenatal plus lactational exposure; birth weight and growth rates through puberty were decreased.[13] Delays have been reported after lactational exposure; weights at pubertal events were not different from those of a normal control group.[14]

Relevant human data are scarce. In a preliminary report, boys exposed before birth to PCBs heavily contaminated with polychlorinated dibenzofurans in the Yucheng poisoning in Taiwan had reduced penile length, although testicular volume and pubertal stages were unaffected.[15] Weight was not different, but height and lean mass were decreased. These children had been smaller at birth, also.[16] A study of children in Michigan showed smaller weights both at birth and at 4 years associated with transplacental PCB exposure.[16] A recent study showed earlier menarche among breast-fed girls with higher transplacental exposure to a related group of chemicals, polybrominated biphenyls.[17]

We have been studying the possible effects of exposure to background levels of PCBs and DDE, both transplacentally and through breast milk, in a birth cohort of children. No effects of exposure on birth weight or on growth in the first year of life were seen.[18,19] We examine here associations between perinatal exposures and pubertal growth and development.

METHODS

The North Carolina Infant Feeding Study was a prospective longitudinal study of children born between 1978 and 1982 and monitored clinically and developmentally until age 5 years.[18-20] The children were from the general population and had no special exposure. In December 1992 we began a puberty follow-up of these children.

We sent annual questionnaires in which we requested height, weight, whether menstruation had begun, current stage of puberty, and whether there was anything unusual about the child that would affect growth and development. We asked that height be measured by having the child stand barefoot against a wall, marking the wall at the top of the child's head, and measuring the height with a tape measure that we provided. Weight without shoes was measured on their own scales. The Tanner stages of puberty are based on a series of pictures of secondary sexual characteristics that appear as an ordered progression from stage 1 (prepubertal) to stage 5 (adult); girls have scales for breast and pubic hair development, whereas boys have scales for genital and pubic hair development. We sent a modification in which line drawings rather than pictures were used[21]; respondents were asked to indicate which stage was closest to their current development. Either the parents, the child, or both supplied information; we used the information supplied by the child when it was available and that from the parent otherwise. Children were monitored for a maximum of 5 years; follow-up was discontinued if they attained the final pubertal stages (according to both child and parent if both supplied information) and, if female, had begun menstruation.

Exposures were estimated as in previous studies of this cohort. PCBs and p,p'-DDE were measured in breast milk, maternal blood, cord blood, and placenta. An index of transplacental exposure that was an estimate of maternal concentration was constructed.[20]

Table I. Adjusted mean height and weight by transplacental exposure categories

		Sample size	Height (cm)	Weight (kg)
Girls, PCB	0-1 ppm	22	165.4 ± 1.6	51.6 ± 1.9
	1-2	178	163.6 ± 0.5	53.0 ± 0.6
	2-3	85/87	163.5 ± 0.8	52.9 ± 0.9
	3+	27	164.2 ± 1.3	57.0 ± 1.6
	P value		.75	.090
DDE	0-1 ppm	19/18	162.4 ± 1.7	54.2 ± 2.1
	1-2	97	163.7 ± 0.7	52.5 ± 0.8
	2-3	100/103	163.5 ± 0.7	54.0 ± 0.8
	3-4	55	164.6 ± 0.9	53.3 ± 1.1
	4+	41	164.0 ± 1.2	51.5 ± 1.4
	P value		.81	.51
Boys, PCB	0-1 ppm	17	169.0 ± 2.0	59.6 ± 2.2
	1-2	165/163	168.9 ± 0.6	56.9 ± 0.7
	2-3	65	169.8 ± 1.0	56.8 ± 1.1
	3+	30	166.2 ± 1.5	56.1 ± 1.6
	P value		.24	.64
DDE	0-1 ppm	21/20	163.9 ± 1.8	53.7 ± 2.0
	1-2	75	168.3 ± 0.9	56.1 ± 1.0
	2-3	80	169.6 ± 0.9	57.4 ± 1.0
	3-4	56/55	169.0 ± 1.1	55.6 ± 1.2
	4+	45	170.2 ± 1.3	60.6 ± 1.4
	P value		.054	.025

Entries are adjusted mean heights and weights at age 14 years and their standard errors. Sample size is number of children with height/weight measurements.

Table II. Adjusted mean height and weight by lactational exposure categories

		Sample size	Height (cm)	Weight (kg)
Girls, PCB	Bottle	30/31	166.1 ± 1.3	55.9 ± 1.5
	0-5 mg	136	162.9 ± 0.6	53.1 ± 0.7
	5-10	107/106	164.1 ± 0.7	52.4 ± 0.8
	10+	37/39	164.0 ± 1.1	53.5 ± 1.3
	P value		.13	.22
DDE	Bottle	30/31	166.1 ± 1.3	55.9 ± 1.5
	0-5 mg	114/113	163.2 ± 0.6	53.4 ± 0.8
	5-10	99/100	163.5 ± 0.7	52.5 ± 0.8
	10-15	43/44	163.4 ± 1.1	53.2 ± 1.2
	15+	24	165.1 ± 1.4	51.4 ± 1.7
	P value		.25	.26
Boys, PCB	Bottle	30/29	169.0 ± 1.5	55.9 ± 1.6
	0-5 mg	128/127	168.4 ± 0.7	57.3 ± 0.8
	5-10	88	169.0 ± 0.8	56.5 ± 0.9
	10+	29	169.3 ± 1.5	57.2 ± 1.6
	P value		.92	.85
DDE	Bottle	30/29	169.0 ± 1.5	55.9 ± 1.6
	0-5 mg	107/106	168.3 ± 0.8	57.0 ± 0.8
	5-10	77	167.6 ± 0.9	56.9 ± 1.0
	10-15	35	170.8 ± 1.3	57.2 ± 1.5
	15+	26	171.0 ± 1.5	56.9 ± 1.7
	P value		.16	.98

Entries are adjusted mean heights and weights at age 14 years and their standard errors. Sample size is number of children with height/weight measurements.

This estimate was an average of the concentration of chemical in all available samples; before averaging was done, values below the detection limit were imputed as the expected value of a log-normal distribution conditional on being below the detection limit, and all concentrations were rescaled as equivalents of parts per million in milk fat at birth. An index of lactational exposure that was an estimate of total milligrams consumed by the child was also constructed.[19] This estimate was based on both maternal concentration and duration of breast-feeding; consumption was assumed to be one amount while the child was mostly breast-fed and half that amount from that time until breast-feeding ended.

For height and weight we fit regression models with the SAS procedure Mixed.[22] All models included age as a cubic polynomial; a cubic was used to accommodate the flattening of the relationship at higher ages. Models also included a linear effect of maternal (usual prepregnancy) weight and a term for white versus nonwhite race. Maternal height and paternal size were not available. For weight, models also included a cubic effect of height. Models also included effects for various categories of exposure, breast-feeding, or both. Breast-feeding was included when possible, because breast-fed children tend to be lighter, at least at young ages.[19,23] When transplacental exposures were evaluated, PCBs, DDE, and weeks mostly breast-fed were all included in the model. When lactational exposures were evaluated, simultaneous examination of these 3 factors was inappropriate because of the high correlations among them, so either PCBs or DDE alone were included in the model, and breast-feeding was not included. Simultaneous examination of transplacental and lactational exposures was not possible because of high correlations. All models accounted for the correlation between measurements on the same child by inclusion of a random term for each child. The *P* values listed in the results are tests for whether the PCB or DDE groups were significantly different from each other in these regression models. Differences were considered statistically significant at $P < .05$ (2-sided).

The age at attainment of each pubertal stage (or at onset of menstruation) was not directly observed but was interval censored. That is, for each child the age at attainment of any stage was known to be either before the age at first contact, between the ages at one contact and the next, or after the age at last contact. This information can be used in a fashion similar to the familiar right-censored survival study, in which length of survival is either known exactly or known to exceed some censoring time. We assumed that the distribution of ages at attainment of stages was normal, with mean depending on exposures and covariates. We obtained maximum likelihood estimates of regression parameters with the SAS procedure Lifereg.[22] As with height and weight, transplacental PCBs, transplacental DDE, and weeks mostly breast-fed were included simultaneously in a model, whereas lactational PCBs and DDE were considered in separate models. Models included adjustment for race.

The study was approved by the Institutional Review Board at the National Institute of Environmental Health Sciences. The study was explained in a letter that accompanied the mailings, and consent was signified by return of questionnaires.

RESULTS

Descriptive Statistics

We attempted to reestablish contact with all of the 856 children from the original cohort who had participated past birth, had exposure information,

Table III. Adjusted mean ages at attainment of pubertal stages (years) by transplacental exposure categories

Girls		n	M	B3	B4	B5	H3	H4	H5
PCB (ppm)	0-1	20-22	12.7	11.1	13.2	16.3	12.0	12.8	14.0
	1-2	176-179	13.0	11.4	13.1	15.5	12.2	12.9	14.1
	2-3	86-87	13.0	11.6	13.0	15.6	12.1	12.7	13.8
	3+	25-28	12.6	10.1	13.0	14.7	10.5	12.2	13.5
P value			.46	.41	.91	.14	.31	.29	.33
DDE (ppm)	0-1	19	13.3	11.6	12.8	15.4	11.9	12.5	14.1
	1-2	95-98	13.0	11.8	13.0	15.5	12.2	12.8	14.5
	2-3	100-103	13.0	11.4	13.1	15.5	12.2	12.9	14.1
	3-4	54-55	13.2	11.6	13.2	15.6	12.1	12.8	14.1
	4+	39-41	12.9	11.0	13.1	14.6	11.3	12.7	14.0
P value			.83	.65	.89	.35	.53	.86	.41
Boys		**n**	**G3**	**G4**	**G5**	**H3**	**H4**	**H5**	
PCB (ppm)	0-1	12	13.0	13.8	16.9	13.1	13.4	15.3	
	1-2	148	12.5	13.6	15.8	13.0	13.6	15.6	
	2-3	59	12.6	13.9	16.1	13.1	13.8	15.7	
	3+	25	12.4	13.4	15.4	13.1	13.6	15.3	
P value			.78	.56	.27	.93	.83	.84	
DDE (ppm)	0-1	15	12.6	13.8	15.6	12.9	13.7	15.3	
	1-2	72	12.4	13.5	15.8	12.7	13.6	15.7	
	2-3	68	12.5	13.6	15.8	13.0	13.6	15.6	
	3-4	48	12.2	13.5	15.7	12.8	13.6	15.4	
	4+	41	12.5	13.7	16.0	12.8	13.7	15.8	
P value			.95	.87	.96	.93	.98	.83	

Entries are adjusted mean ages at attainment of stages; standard errors were generally 0.2 to 0.4 but ranged as high as 0.9 in the smaller groups. Sample sizes vary because some girls did not give information on all 3 aspects (menses, breast stage, hair stage).
M, Menses; *B*, breast; *H*, pubic hair; *G*, genital.

and were not known to be dead. Of those, we had no valid address for 94, the families of 38 refused, and another 124 did not respond to repeated mailings. The remaining 600 children participated. Those who did not participate had similar transplacental PCBs (mean 2.0 vs 1.9), had somewhat higher transplacental DDE (mean 3.3 vs 2.9), and were more likely to have been bottle-fed (16% vs 10%). We excluded from the analysis 6 children who reported conditions or medications likely to affect their pubertal growth or development (growth hormone deficiency, diabetes, or chronic corticosteroid use for Crohn's disease or asthma). The final analysis group had 594 children, 316 girls and 278 boys.

Age at first contact ranged from 10 to 15 years, with most 12 to 14 years old. Duration of participation varied from 1 to 5 years; participation was ended by attaining the final stages of puberty (52% of girls, 32% of boys), death (1 girl, 1 boy, both in accidents), end of study (15% of girls, 8% of boys), or decision of the family to end participation (33% of girls, 60% of boys). Those who continued until the planned end of the study and those who did not had similar transplacental PCBs and DDE and were equally likely to have been bottle-fed.

When first contacted, 85% of the girls were at breast stage 3 or higher; 73% of the boys were at genital stage 3 or higher. At last contact 60% of the girls were at breast stage 5; 45% of the boys were at genital stage 5. At first contact 60% of girls had begun menstruation; 94% had begun by last contact.

The mean height at age 12 years was 158 cm for both sexes; at age 16 years the mean height was 168 cm for girls and 180 cm for boys. The mean weight at age 12 years was 48 kg; at age 16 years the mean weight was 56 kg for girls and 71 kg for boys. Weight was more variable than height; coefficients of variation at a specific age and sex were approximately 20% for weight and 5% for height.

The transplacental PCB index ranged from 0.5 to 5.5 ppm, with a median of 1.7 ppm. That for DDE ranged from 0.3 to 23.8 ppm, with a median of 2.4 ppm. Ninety percent of the children were breast-fed; the length of time during which the child was reported to be mostly breast-fed ranged from 0 to 91 weeks, with a median of 26 weeks. The lactational PCB index

Table IV. Adjusted mean ages at attainment of pubertal stages (years) by lactational exposure categories

Girls		n	M	B3	B4	B5	H3	H4	H5
PCB (mg)	Bottle	31	12.9	11.9	13.5	15.3	12.6	12.9	14.1
	0-5	134-137	12.8	11.4	13.0	15.4	11.6	12.3	13.9
	5-10	104-107	13.0	11.5	12.9	15.7	11.9	12.6	14.1
	10+	36-39	12.8	11.6	13.1	14.9	11.7	12.4	13.7
P value			.69	.69	.47	.29	.08	.24	.65
DDE (mg)	Bottle	31	12.9	11.9	13.5	15.3	12.6	12.9	14.1
	0-5	113-115	12.9	11.5	12.9	15.5	11.6	12.3	13.9
	5-10	97-100	12.9	11.6	13.2	15.4	11.9	12.6	14.2
	10-15	42-44	13.0	11.3	12.7	15.3	12.0	12.5	13.5
	15+	22-24	12.7	10.1	13.3	15.4	11.4	12.6	13.9
P value			.95	.37	.19	.98	.10	.44	.17
Boys		**n**	**G3**	**G4**	**G5**	**H3**	**H4**	**H5**	
PCB (mg)	Bottle	26	12.4	13.5	15.4	12.9	13.5	15.1	
	0-5	110	12.1	13.4	15.4	12.5	13.3	15.2	
	5-10	82	12.7	13.7	15.8	12.9	13.8	15.6	
	15+	24	11.5	13.1	15.4	12.5	13.3	15.2	
P value			.07	.26	.53	.35	.13	.32	
DDE (mg)	Bottle	26	12.4	13.6	15.4	12.9	13.5	15.1	
	0-5	93	12.3	13.6	15.3	12.6	13.4	15.2	
	5-10	72	12.5	13.5	16.0	12.8	13.7	15.6	
	10-15	26	12.0	13.2	15.1	12.7	13.6	15.3	
	15+	25	12.0	13.6	15.9	12.5	13.4	15.6	
P value			.77	.90	.10	.91	.80	.54	

Entries are adjusted mean ages at attainment of stages; standard errors were generally 0.1 to 0.3 but ranged as high as 0.9 in the smaller groups. Sample sizes vary because some girls did not give information on all 3 aspects (menses, breast stage, hair stage).
M, Menses; *B*, breast; *H*, pubic hair; *G*, genital.

among the breast-fed infants ranged from 0.2 to 23.1 mg, with a median of 5.0 mg. That for DDE ranged from 0.2 to 96.3 mg, with a median of 6.2 mg.

Relation of Outcomes to Exposures

Adjusted mean heights and weights for each category of transplacental PCB and DDE exposure are shown in Table I. Weight is adjusted for height. For boys height and weight varied among the DDE categories, with those with the highest exposures being heavier than those with the lowest by 6.9 kg and taller by 6.3 cm. Neither height nor weight differed significantly among PCB categories. For girls weight increased with transplacental PCB exposure, but neither this effect nor any others were statistically significant.

Comparable results for lactational exposures are shown in Table II. Differences among categories were smaller than for transplacental exposure and were not significant.

Adjusted mean ages at attainment of pubertal stages for each category of transplacental exposure are shown in Table III. There was some tendency for girls with higher transplacental PCB or DDE exposures to mature earlier, but the differences were not significant. Boys showed little pattern. Comparable results for lactational exposures are shown in Table IV. Girls who were bottle-fed tended to mature later, but again, differences were not significant.

Black children in this cohort had much higher transplacental DDE exposures than did white children.[20] Black girls have also been shown to mature earlier than white girls.[24] If 25 non-white children were excluded from the analyses, results were generally similar; the effect of transplacental PCB exposure on the weight of girls was slightly larger and was significant at $P = .046$.

DISCUSSION

DDT as applied was a mixture of chemicals with varying properties. We measured only p,p'-DDE; in areas where no active spraying is occurring, this is the major compound detected, with other members of the DDT family being present at much lower concentrations. Compounds in this family have a variety of actions. P,p'-DDE has been reported to be a potent androgen

receptor antagonist.[3] O,p'-DDT has estrogenic properties, as do several other members of the DDT family.[1] P,p'-DDT, p,p'-DDE, and others induce mixed-function oxidase enzymes, which in turn metabolize endogenous steroids[1]; this can lead to apparent antiestrogenic effects. The multiple actions of these agents and the inconsistency of pubertal effects seen in the literature led to uncertainty about the direction of effects that might be expected in this study.

PCB exposure is also to a mixture of congeners. Our measure of PCBs was a summary measure of total PCBs; because levels of the most commonly seen congeners tend to be correlated in humans, those with the highest totals would have been likely to have high levels of most of these congeners. PCBs also have multiple actions. Some congeners display estrogenic effects, and some display antiestrogenic effects.[2] PCBs are also inducers of a wide variety of enzymes and disrupt thyroid hormone homeostasis in a variety of ways.[2]

We saw effects of prenatal exposure but not of lactational exposure, although the correlation between them makes it impossible to separate the effects completely. Much larger amounts of chemical are transferred through lactation than are transferred across the placenta. However, cross-fostering experiments in animals have shown that effects can be specific to type of exposure. Bjerke and Peterson[25] exposed male rats to tetrachlorodibenzodioxin; they showed that only transplacental exposure caused pubertal delay and decreased sperm production, whereas only lactational exposure caused feminization of behavior. Behavioral toxicity of PCBs in rats has also been shown to be specific to prenatal exposure,[26] and results in humans are similar.[16]

Onset of puberty, including physical growth and development of secondary sexual characteristics, is controlled by a complex series of neuroendocrine events. Growth and pubertal development are generally concomitant, although disassociations can occur. We saw significant effects on physical growth only. Possibly growth alone is affected; alternately, our measures of pubertal development, which divide a continual process into a few stages, are likely to be less sensitive than our measures of growth, so that effects could have been missed. For pubertal stages we relied on assessment by the children or their parents. Studies assessing the ability of children to rate themselves have generally shown moderate to good agreement with physician assessment,[21,27-30] but misclassification is possible.

We saw different effects in the 2 sexes. There was no obvious reason to expect sexually dimorphic responses. Prenatal PCB and DDE exposures were correlated, which would make it possible to confuse an effect of one with an effect of the other; however, the correlation was moderate (r = 0.25), and the analyses included both exposures.

The members of this cohort were not a random sample. For example, the mothers of the children tended to be well educated, and a high proportion of the children were breast-fed.[20] A more serious concern involves differential follow-up. From the target population we obtained puberty information on 70%. The nonrespondents differed somewhat in their exposures, and we have no information about their pubertal development. Of those who did participate, 67% of girls and 40% of boys continued until the planned end of the study. Those who continued were similar in their exposures to those who did not. The most likely explanation for failure to participate or to continue participation is simple lack of interest. However, children with unusual development could have had either more or less interest in the study than children with normal development.

We have shown a relationship between prenatal exposures at background levels and increases in adolescent weight and height. This is an observational rather than an experimental finding and thus is subject to possible uncontrolled bias and confounding. Furthermore there is no clear biologic mechanism explaining the findings. If the findings are confirmed in other studies, it would be an important observation about the effects of these chemicals.

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